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During the last FY of the award, the Cancer Institute of Long Island benefited from CPMRP funding in a manner consistent with the proposed activities of the award. In the area of core instrumentation acquisition, an Applied Biosystems Genetic Analyzer Model 3730 was acquired. The instrument is situated in the University DNA Sequencing Facility, operated by the School of Medicine. The facility serves cancer institute research laboratories of the School of Medicine. It has a subscription base of more than 100 active users. A new, state-of-the-art imaging system was requested via programmatic modification that was submitted and approved by CDMRP under separate cover; a Carl Zeiss Fluorescence Correlation Spectroscopy (FCS) Confocal Microscope, scheduled for delivery in October 2003. A Professional Engineer level optical engineer will be assigned to operate this new instrumentation. This system is capable of examining and measure single molecule activities. This microscope, like its predecessor Multi-Photon Confocal system (purchase in year-02) will be housed in a class 10,000 (ISO level 7) clean room. The aforementioned Carl Zeiss Inverted Multi-Photon system is now on-line, and operating to specification. Following an extensive national search, a high-level microscopist was hired to operate this system. He is now fully trained and serving the Cancer Institute research faculty at Stony Brook.

Consistent with the funding for this initiative were the granting of multi-year RSU packages, or Research Support Units. RSU's are a mechanism to ensure the protection of time for junior faculty and work as enhancements to enable the successful establishment of their laboratories. Each RSU provided support for laboratory personnel, small or specialized research equipment, and supplies. During the last funding year two individuals were recruited into this initiative. The faculty designees for this activity are Howard Adler, MD, Assistant Professor of Urology, and Howard Crawford, Ph.D., Assistant Professor of Pharmacological Sciences. Dr. Adler is investigating the angiogenesis of prostate cancer from a translational approach. Dr. Crawford continues to make significant strides in understanding cell and protein signaling events in pancreatic and breast cancer. The RSU's supported faculty are required to have mentors from the senior faculty. Both Drs. Adler and Crawford mentors are well-established, extramurally funded cancer investigators.

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**Introduction:**

The State University of New York at Stony Brook, School of Medicine continues to develop its infrastructure for to support a Comprehensive Cancer Center in central Long Island, New York. Achievements vital to this year of CDMRP funding are summarized below. CDMRP funding focused in cancer research infrastructure has greatly assisted the efforts of the School of Medicine by enabling our ability to provide a foundation for aspiring young scientists. Drs. Adler and Crawford continued to receive base support from this mechanism as they further develop their research laboratories. CDMRP funds allocated towards core technologies have enabled the School of Medicine to secure and bring on-line a new state-of-the-art Multi-Photon Imaging System, and a High-Throughput Genetic Analyzer. A FCS Confocal Microscope was ordered via CDMRP support as well. These instruments are available as cancer research center core instruments and are operated by skilled technicians. The instruments are centrally sited, and are supported by ancillary equipment made available by the School of Medicine via other funding sources (not CDMRP).

**Body:****Cancer Invasion & Angiogenesis - Dr. Howard Adler, MD, Assistant Professor of Urology:****Evaluating the Role of Matrix Metalloproteinases in Prostate Cancer Progression-**

Working in collaboration with Drs. Stan Zucker (Research Mentor) and Jian Ciao. The goal of this project is to examine the role of membrane type 1-matrix metalloproteinase in prostate cancer progression and metastasis by establishing a stable LNCaP (an androgen dependent cell line which does not produce endogenous type-1 matrix metalloproteinase, MT1-MMP) cell lines expressing MT1-MMP/GFP chimera and a GFP control.

The initial goal: to examine the role of membrane type 1-matrix metalloproteinase in prostate cancer progression and metastasis by establishing a stable LNCaP (an androgen dependent cell line which does not produce endogenous type-1 matrix metalloproteinase, MT1-MMP) cell lines expressing MT1-MMP/GFP chimera and a GFP control.

- 1) 2x10<sup>6</sup> stable cells expressing GFP and MT1/GFP were injected orthotopically into four-week old NCI/nu male mice. Each group contained 10 mice.
- 2) Five mice (2 from GFP group and 3 from MT1/GFP group) died the next day.
- 3) Weight changes:
  - A) A week later after prostate injection (2-11-03), weight gain from the MT1/GFP group was slower than that of the GFP group. The mean of weight gain for GFP group was 4.11g, while the mean of weight gain for MT1/GFP group was 3.72. This result is consistent with the weight gain from subcutaneous tumor injection groups.
  - B) The weight loss from both groups began week 8 after injection until sacrifice at week 11.
- 4) All mice were sacrificed at week 11.
  - A) GFP group:
    - a) tumorigenesis: two out of eight mice had prostate tumors; four mice had tumors but outside the prostate; no tumors were found in the two other mice. b)

All tumors have green fluorescence under UV light indicating expression of GFP/LNCaP cells. c) No visible enlarged lymph nodes were detected. No metastatic cells were found under fluorescent microscopy. d) No tumor nodules were found on the surface of the lungs. However, most of the mice had micro-metastasis (a single cell or a few cells) in the lung under fluorescent microscopy; this data suggests LNCaP cells orthotopically injected into the prostate can undergo metastasis to the lung. The determination of lung metastasis needs a sensitive approach, such as the GFP marker to detect it (previous reports denied tumor metastasis of LNCaP cells). e) No metastatic cells in liver or kidney. f) Sections from different organs are currently under examination.

5) B) MT1/GFP group:

a) tumorigenesis: three out of 7 had tumor growth (one in an early stage). b) All tumors had green fluorescence under UV light. c) Lymph nodes from tumor bearing mice were examined; however, no metastatic tumor cells (GFP fluorescence) were detected. d) No tumor nodules were found on the surfaces of lungs; however, large tumor emboli and metastatic tumors were found in the lung. Compared to metastatic tumor in the lung from GFP group, there were more metastatic tumors in MT1/GFP group. e) No metastatic cells were detected in liver and kidney. f) Sections from different organs are currently under examination.

The plan is to continue to increase experimental groups for high, medium and low expression of MT1-GFP/LNCaP. It is expected that repeat experiments will lead to better results as experience with establishing orthotopic tumors increases.

The CDMRP support for Dr. Adler has enabled him to obtain the necessary mentorship, research funds, and protected time to achieve his academic goals. He attends and routinely participates in weekly laboratory meetings held in Dr. Zucker's laboratory at the Northport Veterans Administration Hospital, and the Cancer Institute of Long Island research meetings. Dr. Adler has been able to improve his abilities to critically evaluate research at the basic science level. There is true potential for translation of this project as it matures towards completion. Through new collaborations with other cancer investigators, Dr. Adler has been able to provide his colleagues with orthotopic prostate cancer models. His training in GU cancers has made his contribution even more distinct in research that seeks to evaluate the chemokine regulation of prostate cancer metastasis and investigate potential new therapeutic modalities for prostate cancer.

***II) Dr. Howard Crawford, PhD, Assistant Professor Pharmacological Sciences:  
Signal Transduction – Matrix Metalloproteinase-7***

Matrix metalloproteinase-7 (MMP-7) has been shown to contribute to both the formation and invasion of adenocarcinomas in several glandular tissues. MMP-7 expression is highly restricted in normal tissue, but is frequently found in tumor cells of benign and well-differentiated invasive tumors of the breast, intestine, prostate, esophagus, stomach and pancreas. Dr. Crawford's research focuses on the role of MMP-7 in pancreatic cancer, the 5<sup>th</sup> most common cause of cancer-related death in the United States. We have found that MMP-7 is expressed by the tumor cells in 98% of pancreatic ductal adenocarcinoma (PDAC) patient samples examined, by far exceeding the frequency of MMP-7 expression in tumors of other tissues. MMP-7 expression ranges from the

earliest stages of tumor formation through to invasive carcinoma. Strikingly, MMP-7 was also expressed by metaplastic duct epithelium in 100% of PDAC samples examined. Metaplastic duct epithelium, particularly that formed in the context of chronic pancreatitis (CP), has been hypothesized to act as a tumor precursor. With this in mind, we found that MMP-7 is expressed in the metaplastic ducts of 93% of CP samples. Most importantly, by inducing CP in mice that have had the MMP-7 locus inactivated by homologous recombination, we find that all aspects of CP are severely inhibited, including the formation of metaplastic duct epithelium. Thus, we surmise that MMP-7 is involved in pancreatic tumor formation through its ability to promote the formation of metaplastic duct epithelium. We propose to systematically dissect the multiple potential roles of MMP-7 in CP and PDAC with particular emphasis on acinar-to-ductal metaplasia.

Dr. Crawford is currently testing the function of MMP-7 in the progression of mouse metaplasia and neoplasia by removing the gene in multiple mouse models of pancreatic cancer under the mentorship of Dr. Jeffrey Pessin, Professor and Chair of Pharmacological Sciences. Simultaneously, we are testing the effectiveness of MMP inhibitors in preventing tumor progression in these models. Finally, we are using in vitro models of pancreatic cancer to identify substrates of MMP-7 that will explain its function in PDAC progression and potentially reveal additional drug targets in the fight against PDAC.

#### ***Cancer Imaging Core Research Support***

To broadly support the research of the five-thematic integrated cancer research programs several new core imaging platforms are moving ahead under various states of maturity. These include (A) Multi-Photon Confocal Imaging System, and (B) the Fluorescence Correlation Spectroscopy (FCS) Confocal Imaging System.

- A) The selected system is an inverted Carl Zeiss Micro-Imaging product equipped with a Coherent Laser Group *Chameleon Laser*. Since the purchase of this system the institution has successfully commissioned a 224 net ft<sup>2</sup> ISO Class 7 clean room. The system is 100% on-line and accepting samples for analysis from the cancer research community. A long and thorough national search was orchestrated by the Office of Scientific Affairs which resulted in the selection of a well-trained confocal (single-photon) microcopist. He has since been trained by Coherent and Carl Zeiss in the realm of *Multi-Photon* image sample manipulation, image acquisition, image deconvolution, and data analysis. The instrument and the staff's expert services are available to the cancer research community. Adjacent to this laboratory is a well equipped, comfortably furnished computer laboratory with three high-speed workstations for post image analysis. The institution has provided matching funds of \$100,000 to develop this aspect of the facility. Three networked PC's, a dedicated file server and three fully licensed copies of Bitplane Imaris are available to the cancer researcher. The Departments of Molecular Genetics & Microbiology, Neurobiology & Behavior, and Pharmacological Sciences, have organized a matching funds package worth \$225,000 for out-year personnel support for this Cancer Institute Initiative.
- B) The selected system is an inverted Carl Zeiss Micro-Imaging product equipped with FCS measurement lasers capable of providing both FRET and FRAP analysis. FCS is a spectroscopic technique for the study of molecular



interactions in solution. FCS monitors the random motion of fluorescently labeled molecules inside a defined volume element irradiated by a focused laser beam. These fluctuations provide information on the rate of diffusion or diffusion time of a particle and this, in turn, is directly dependent on the particle's mass. As a consequence, any increase in the mass of a biomolecule, e.g. as a result of an interaction with a second molecule, is readily detected as an increase in the particle's diffusion time. Not least due to its simple underlying principle, FCS is an ideal approach for the study of thermodynamic and kinetic features of molecular interactions in solution.

FCS imaging technologies are both novel and essential to the growth and invasion of cancer in select tissue types. FCS imaging is crucial to understanding single molecular events and/or insults that are integral to a host of disease states including cancer invasion and metastasis. A specially designed ISO Class 7 clean room is under development to house this system. A dedicated 1.0 FTE PE of optical engineering has been identified to operate this instrumentation. The institution is providing the necessary funds to construction and commission the clean room as well as fund the FTE.

**C) Genomics Instrumentation -**

The selected system is an Applied Biosystems 3730 Genetic Analyzer. This high-throughput instrument is situated in the existing University DNA Sequencing Core. This facility has a long, outstanding service record as an institutional core; managing sophisticated instrumentation and support staff for the cancer Institute of Long Island, and the campus at large. It provides the cancer research community with access to a staff of 2.0 well-trained molecular biology FTE's. Ancillary support instrumentation includes two robotic liquid handling instruments for sample preparation and two Real Time-PCR instruments. The institution provided the support for the RT-PCR instrumentation as dictated needs made it obvious that these instruments be available and on-line prior to what was anticipated at the time of CDMRP funding. The cancer research community was hampered, however, by the through-put capabilities of the existing Applied Biosystems 3100 capillary DNA analyzer. Therefore, it was determined and prioritized that a faster and more sensitive analyzer become available to the faculty. This 3730 replaced the existing 3100 in the winter of 2004. The new instrument is now on-line and operating to specification. The throughput capabilities in this core have been doubled. Dedicated Cancer Institute 96 well micro-titer plates are processed and analyzed throughout the day. This instrument is serving on average 20 separate cancer laboratories daily.

**Key Research Accomplishments:**

The CDMRP funding awarded to Stony Brook via this mechanism is directed towards providing infrastructure support to better serve the needs of the faculty of the Cancer Institute of Long Island, and cancer researchers throughout the campus. Accomplishments for this reporting period include:

- 1) Instrumentation-Carl Zeiss Multi-Photon Confocal Microscope on-line \*.
- 2) Instrumentation- Commissioning the ISO 7 clean room for the Multi-Photon Microscope \*.
- 3) Instrumentation- Recruiting a well trained microcopist to operate the Multi-Photon Microscope \*.

- 4) Instrumentation- Establishment of a high-level image analysis center to support the Multi-Photon Confocal Microscope users \*\*.
- 5) Instrumentation- Acquisition of FEI Philips Digital Transmission Electron Microscope for cancer imaging \*\*.
- 6) Instrumentation- Testing protocols for the Ciphergen Biosystems SELDI Instrument for Cancer Proteomics acquired in 2003.\*\*
- 7) Instrumentation- Benchmarking of the Cancer Tissue Bank Carl Zeiss Laser Capture Microdissection Microscope acquired in 2003 \*\*.
- 8) Instrumentation- Completion, equipping, staffing, and commissioning of a Cancer Institute Tissue Bank Laboratory \*\*.
- 9) Instrumentation- Acquisition of a FCS Confocal Microscope \*.
- 10) Instrumentation- Construction of a ISO 7 clean room for the FCS Confocal Microscope \*\*.
- 11) Instrumentation- Acquisition and installation of an ABI 3730 High-Throughput Genetic Analyzer \*.
- 12) Instrumentation- Acquisition and installation of new MJ Research Real-Time PCR instruments \*\*.
- 13) Instrumentation- Development of protocols to further enhance the throughput capabilities in MALDI-ToF for Cancer Proteomics \*\*.
- 14) Faculty Development- Providing start-up funds enhancement to Dr. Adler via a mentored intramural program \*.
- 15) Faculty Development- Providing start-up funds enhancement to Dr. Crawford via a mentored intramural program \*.
- 16) More than 20 key publications produced by the cancer research faculty in the School of Medicine. A fully annotated citation list is available for review in the appendix of this report \*\*.
- 17) Twenty-two cancer research intramural pilot and feasibility awards issued via the School of Medicine Targeted Research Opportunities Program \*\*.
- 18) Establishment of a new thematic research program in Cancer Chemo-Prevention to include the recruitment of new senior-level faculty (Basil Rigas, MD, Professor, Dept. of Medicine) \*\*.

\*= Benefit derivative of CDMRP funds.

\*\*= Benefit derivative of funds allocated to complement CDMRP initiative at Stony Brook.

### **Reportable Outcomes:**

1- *Research Support Units*- The RSU support provided to Drs. Adler and Crawford are too recent to expect publications in peer-reviewed journals. Both Drs. Adler and Crawford are aware of the requirement to cite CDMRP support in their manuscripts.

2- *Cancer Genomics Core*- To date this facility has provided services that have resulted in thousands of sequences and validations for samples submitted by Cancer Institute researchers. New RT PCR instruments and the Genetic Analyzer are enhancing an already robust and well-respected core facility.

3- *Cancer Imaging Core*- To date the instrumentation for the Multi-Photon capabilities have been benchmarked and are performing to specification.



The FCS instrument will be received in the Fall of 2003 and should fully benchmarked and operational by the winter holidays prior to 2005.

**Conclusions:**

The results of the beneficial infrastructure support that the CDMRP provides to the School of Medicine is funding of the two RSU packages for Drs. Adler and Crawford. The extension of these RSU's for these junior faculty in 2003-2004 have helped them advance their research significantly. CDMRP funds have helped usher in many new, state-of-the-art, platform technologies in cancer research instrumentation.

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Not applicable. CDMRP funding is targeted towards infrastructure support.

**Appendices:**

25 Reprints are available upon request.

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